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(71) Applicant: MJ RESEARCH, INC. [US/US]; 590 Lincoln Street, Waltham, MA 02451 (US).

(72) Inventors: TITCOMB, Paul, S.; 51 Pleasant Street, Sagamore, MA 02561 (US). FINNEY, Michael, J.; 489 Douglass Street, San Francisco, CA 94114 (US). COHEN, David; 203 High Street, Dedham, MA 02026 (US). SMITH, William, J.; 6 Proctor Road, Townsend, MA 01469 (US).

(74) Agent: SULLIVAN, Thomas, M.; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

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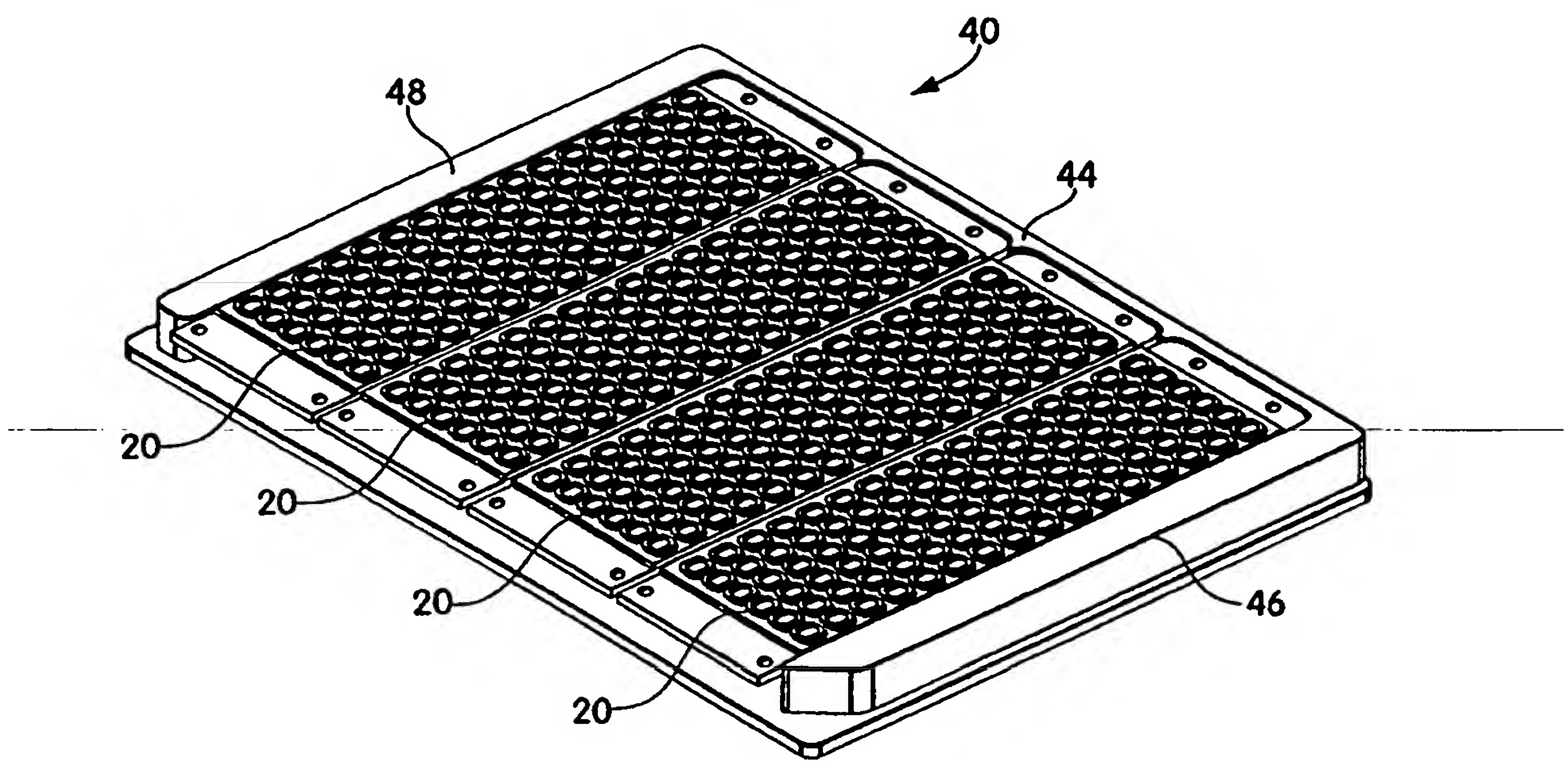

(57) Abstract

An apparatus and method for subjecting samples to thermal cycling. The apparatus includes a cartridge (20) having a body having an upper surface with a length and width each of which is approximately equal to a length and a width of a standard microscope slide, and a plurality of wells formed within the upper surface of the body. The center–to–center spacing between each pair of adjacent wells in the plurality of wells is approximately either 9 mm, an integral fraction of 9 mm, or an integral multiple of 9 mm. In one embodiment, the apparatus includes a holder (40) for holding four of the cartridges (20) to provide filling of the wells using standard equipment designed

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AUTOMATION-COMPATIBLE SLIDE FORMAT SAMPLE CARTRIDGE

Field of the Invention

The present invention relates generally to multiple sample vessels for aqueous test solutions, and more specifically to a method and apparatus for performing multiple sample assays using an improved vessel, having multiple sample wells, and adapted for use with standard thermal cycling apparatus and with standard automated effector equipment.

Background of the Invention

A number of research and clinical procedures and analytical techniques require or desire the use of an array of wells or tubes in which multiple samples can be placed for screening and evaluation and be subjected to thermal cycling. Examples of these techniques/procedures include: polymerase chain reactions (PCR), and primed *in situ* synthesis (PRINS). Prior art multiple sample vessels that provide an array of wells suitable for subjecting aqueous solutions to thermal cycling are known. These prior art vessels typically are one of two types. The first type of prior art vessel has been developed to be compatible with standard automated processing equipment using a known "microplate format" having an 8 by 12 rectangular array of wells (96 sample wells in total) with center-to-center spacing of 9 mm.

MJ Research Corporation of Watertown, MA, the assignee of the present application, has developed a 384 sample well vessel based on the microplate format. The 384 sample well vessel provides 384 wells by reducing the center-to-center spacing of the wells to 4.5 mm, while maintaining the same overall dimensions of the vessel. The 384 sample well vessel 10, shown in Figs. 1A and 1B, includes a 16 by 24 rectangular array of wells 12. Each of the wells is made from a conical-shaped tube, as shown in Fig. 1B, to facilitate heat transfer to the sample during thermal cycling. During thermal cycling, the vessel 10 is placed upon a metal temperature-control block 14, shown in Fig. 1C, that has a number of cavities 15 for receiving each of the wells 12. The control block is heated and cooled to thermal cycle the samples in the wells.

The second type of prior art vessel is essentially a microscope slide onto which a sample is placed. For some samples, such as cellular samples used in *in situ* studies, it is desirable to use a microscope slide as the medium. Some prior art microscope slides include one or more wells for holding one or more samples. There are a number of sample block devices available into which microscope slides may be inserted to provide thermal cycling of the samples. One such sample block device 16 is shown in Fig. 2. The sample block device 16 is designed such that two

of the devices fit within a thermal cycler, such as that available from MJ Research, Inc. of Watertown, MA under Part No. ALD-0211. The sample block 16 is described further in co-pending U.S. Patent Application 08/567,887, assigned to the assignee of the present application, and incorporated herein by reference. The sample block 16 has a number of sample cartridge slots 18 for receiving microscope slides to subject samples on the microscope slides to thermal cycling. Each of the cartridge slots 18 are approximately 70 mm deep, 28 mm wide and 3.5 mm high to accommodate standard microscope slides that are typically approximately 25 mm wide by 76 mm long.

When two sample blocks are used with a thermal cycler, they provide a larger area of thermal control than when the thermal cycler is used with a standard microplate. However, as discussed above, the sample blocks are designed to accommodate microscope slides, and standard microplates have an advantage over microscope slides in that they provide a larger number of sample wells, and the sample wells of standard microplates can be filled and analyzed using existing automated equipment.

It is desirable to provide a multiple sample vessel that can be filled and analyzed using standard automated equipment, and can also be subjected to thermal cycling using sample blocks designed to accommodate microscope slides.

Summary of the Invention

Embodiments of the present invention are directed to an apparatus and method for subjecting samples to thermal cycling.

In a first embodiment, a cartridge for containing samples includes a body having an upper surface with a length and width, each of which is approximately equal to a length and a width of a standard microscope slide, and a plurality of wells formed within the upper surface of the body. In one version of the first embodiment, the center-to-center spacing between each pair of adjacent wells in the plurality of wells is approximately either 9 mm, an integral fraction of 9 mm, or an integral multiple of 9 mm.

In other versions of the first embodiment, the cartridge includes one or more of the following features: each of the wells is at least 2.4 mm deep; each of the wells has a raised rim such that grooves are formed on the upper surface between the wells; each of the wells has a flat, transparent bottom to permit optical inspection of samples contained within the wells; each of the wells has a base that is less than 0.75 mm thick; the wells are arranged in a 6 by 16 array; the cartridge further includes a cover that seals each of the wells; the cover is a multi-layer sheet

having a stiff backing layer, a deformable layer, and may include a hinged section for attachment to the cartridge; and the cover is transparent to allow optical inspection of samples in the wells through the cover.

In a second embodiment of the present invention, a cartridge holder includes a frame having an upper surface, a plurality of cartridges disposed on the upper surface, each of the cartridges including a body having an upper surface with a length and width, and a plurality of wells formed in the upper surface of the body. The plurality of cartridges are arranged on the upper surface of the frame such that the wells of the cartridges form a continuous grid.

In different versions of the second embodiment, the cartridge holder includes one or more of the following features: the center-to-center spacing of wells in the grid is approximately either 9 mm, an integral fraction of 9 mm, or an integral multiple of 9 mm; four cartridges are disposed on the upper surface of the frame; the length and width of each body is approximately equal to a length and width of a standard microscope slide; the wells of each of the cartridges are arranged in a 6 by 16 grid, and the wells of all the cartridges are arranged in a 16 by 24 grid; the frame has a first side, a second side and a back side, each extending above the upper surface; each of the wells is approximately 2.4 mm deep; each of the wells has a raised rim such that grooves are formed between the wells; each of the wells has a flat transparent bottom; and at least one of the cartridges has a handle section extending beyond the upper surface to allow the cartridge to be grasped for placement in and removal from the cartridge holder.

A third embodiment of the present invention is directed to a method of thermal cycling samples including steps of loading a plurality of cartridges into a cartridge holder, each of the cartridges having a plurality of wells arranged in a first grid, filling each of the wells with a sample, loading each of the cartridges into a thermal block, subjecting the samples to thermal cycling, removing the cartridges from the thermal block, and analyzing the samples.

In different versions of the third embodiment, the method includes one or more of a number of features including: the step of loading includes a step of arranging the cartridges in the cartridge holder such that the wells of the cartridges form a second grid; the second grid includes 384 wells arranged in a 16 by 24 array; the wells in the second grid have a center-to-center spacing of approximately either 9 mm, an integral fraction of 9 mm, or an integral multiple of 9 mm; each of the cartridges has a length and width, each of which is approximately equal to a length and width of a standard microscope slide; each of the wells has a transparent flat bottom; the step of analyzing includes a step of optically inspecting the samples through the bottom of the well; and the method further includes a step of sealing each of the wells using a cover.

Brief Description of the Drawings

For a better understanding of the present invention, reference is made to the drawings which are incorporated herein by reference and in which:

Figs. 1A and 1B show a multiple well vessel in accordance with the prior art;

Fig. 1C shows a temperature control block used with the multiple well vessel shown in Figs. 1A and 1B.

Fig. 2 shows a sample block used for thermal cycling samples contained on microscope slides.

Fig. 3 shows a perspective view of a sample cartridge in accordance with one embodiment of the present invention;

Fig. 4 shows a top view of the sample cartridge of Fig. 3;

Fig. 5 shows a cross-sectional view of the sample cartridge of Fig. 3 taken along lines A-A of Fig. 4;

Figs. 6A, 6B and 6C show different embodiments of covers for the cartridge shown in Fig. 3.

Fig. 7 shows a perspective view of a cartridge holder in accordance with one embodiment of the present invention;

Fig. 8 shows a perspective view of the cartridge holder of Fig. 7 with four sample cartridges contained therein;

Fig. 9 shows a second perspective view of the cartridge holder of Fig. 7 with four sample cartridges contained therein; and

Fig. 10 shows a flow chart of a process for conducting thermal cycling of samples in accordance with one embodiment of the present invention.

Detailed Description

One embodiment of a sample cartridge 20 will now be described with reference to Figs. 3, 4 and 5. The sample cartridge 20 has a length L of approximately 84 mm, a width W of approximately 27 mm, and a height H of approximately 3 mm. Therefore, the sample cartridge 20 is of approximately the same width and slightly longer than a standard microscope slide. The sample cartridge 20 has a top surface 22 having a 6 by 16 array of sample wells 24. The cartridge has thin flat sections 26 and 28 at each end of the cartridge, and has a flat bottom surface 30. The thin flat sections 26 and 28 allow the cartridge to be easily handled and

transported by automated equipment, such as a robotic arm, without the robotic arm coming in contact with the wells 24.

In the embodiment of the invention shown in Figs. 3-5, the sample wells 24 have a center-to-center spacing of 4.5 mm, and there are a total of 96 wells. In another embodiment, a sample cartridge has a total of 24 sample wells formed in a three by eight array with center-to-center spacing of 9 mm.

Each of the wells 24 in the cartridge 20 is open at the top surface of the cartridge, has a substantially uniform rectangular cross section with rounded corners as best shown in Fig. 4, has a depth of approximately 2.4 mm and a volume of approximately 12 mm^3. Around each of the wells 24 in the cartridge is a raised rim 25. The raised rims improve sealing and reduce the possibility of contamination between wells by creating recessed areas 27 between each of the wells.

The cartridge 20 is designed to fit within one of the cartridge slots 18 of the sample block device shown in Fig. 2 to allow thermal cycling of samples contained within the sample wells. To properly accommodate the cartridge 20, the sample block device may be manufactured with slightly larger openings. During thermal cycling, it is desirable to provide an air tight seal over each of the wells to prevent water vapor from escaping from the wells causing a loss in sample volume. Any loss in volume in a sample may change the concentration of reaction components in the sample and invalidate test results. It is also desirable to isolate each of the wells to prevent cross-contamination of the samples. In addition, it is desirable that the air tight seal be removable to allow access to the wells after thermal cycling for testing of the samples. The air tight seal must be sufficiently thin to allow the cartridge to fit within one of the cartridge slots of the block device.

In one embodiment of the present invention, the cartridge 20 is sealed using one of the techniques and materials described in co-pending U.S. Patent Application No. 08/337,160, which is assigned to the assignee of the present invention, and incorporated herein by reference. This sealing technique will now be described with reference to Fig. 6A which shows a perspective view of the cartridge 20 with a multi-layer composite sheet 32 disposed above the cartridge. The multi-layer sheet 32 includes a backing layer 34 and a sealing layer 36. The backing layer provides strength and uniformity to the sealing layer, and in one embodiment, is made from a flexible material such as polyester film to allow easy application and removal of the multi-layer sheet 32. The sealing layer 36 is made in one embodiment from an inelastically deformable material such as silicone so that the sealing layer can deform to account for any differences in the

height of the wells and to fit in the grooves between wells to provide an air tight seal. The surface of the sealing layer that contacts the upper surface of the cartridge is sufficiently tacky to adhere to the cartridge, yet can be readily removed to allow testing of the samples in the wells. In one embodiment, the multi-layer sheet may be easily penetrated with a hyperdermic syringe for testing of samples, and the multi-layer sheet is transparent to allow observation of the samples.

Fig. 6B shows an alternate embodiment of a cover 32A for the cartridge 20. The cover 32A, similar to cover 32, includes a backing layer 34A and a sealing layer 36A. Cover 32A differs from cover 32 in that it is flexible to allow the cover to be easily placed on and removed from the cartridge 20.

Fig. 6C shows another alternate embodiment of a cover 32B for the cartridge 20. The cover 32B is attached to the cartridge 20 using a hinge 33. The hinge is formed by extending a portion 35 of the backing layer 34B beyond the sealing layer 36B, and attaching the extended portion 35 to one of the flat sections 26 or 28 of the cartridge using an adhesive or some other known technique. The use of the hinge allows the cover to remain with the cartridge when the cover is lifted off of the wells. The hinged cover 32B may be implemented using either the flexible cover 32A shown in Fig. 6B or the rigid cover shown in Fig 6A.

In one embodiment of the present invention, the multi-layer sheet is sealed to the cartridge 24 by placing a flat block over the top of the multi-layer-sheet and providing sufficient downward force on the block to cause the sealing layer to deform into the wells and grooves of the cartridge.

Fig. 7 shows a cartridge holder 40 used for holding cartridges 20 during automated filling of the cartridge wells 24 and during testing and evaluation. Fig. 8 shows the cartridge holder 40 with four cartridges 20 contained within the holder, and Fig. 9 shows the cartridge holder 40 with 3 cartridges 20 loaded in the cartridge holder and with a fourth cartridge partially loaded in the cartridge holder. The cartridge holder has a working surface 42 having an area that is sized to accommodate four cartridges 20 adjacent to each other. While the working surface could be sized to accommodate a number of cartridges other than four, the use of four cartridges results in a 16 by 24 well array, with wells at 4.5 mm centers, that is compatible with standard automated processing equipment.

The cartridge holder 40 has a first side rail 46, a second side rail 48 and a back rail 44 that hold the cartridges tightly against each other to provide 4.5 mm spacing between adjacent wells on adjacent cartridges. An opening 50 is provided at one edge of working surface to allow the

cartridges 20 to be easily loaded into and removed from the cartridge holder as shown in Fig. 9. The back rail 50 includes three notches 52 that help to maintain each of the cartridges in its proper location on the working surface 42. As shown in Fig. 4, each of the cartridges 24 has rounded corners 29 and 31 on the flat section 28. Each notch 52 fits between a rounded corner 29 of one cartridge and a rounded corner 31 of a second cartridge.

In one embodiment of the present invention, the cartridge holder is made, using a mold, from a material such as polycarbonate plastic however, other suitable, sufficiently rigid materials could also be used. In this embodiment, the cartridges 20 are also made from a mold, so that the wells 24 are integrally formed within the cartridge to prevent any leaking of the samples. The cartridges are made using a material such as polypropelene plastic. Other materials could also be used to make the cartridges 20, however, it is preferable to use a transparent or semi-transparent material to allow optical analysis of the samples through the flat bottom of the cartridge. Instead of using a mold, the cartridges may also be machined from a block of material with each of the wells being formed by drilling the proper size wells in the block.

A process 100 for using the cartridges 20, cartridge holder 40, and the thermal block 16 to perform automated thermal cycling of samples will now be described with reference to Fig. 10. In a first step 110, four cartridges 20 are loaded into the cartridge holder 40 using a robotic arm. Prior to their loading into the cartridge holder, the cartridges 20 may be held in a stack or some other configuration. The sample wells are then filled in step 120 with samples using an automated dispensing machine such as a Biomeck-2000 Sample Processor available from Beckman Instruments, Brea, CA. In step 130, a multi-layer sheet is used to cover each of the cartridges as described above. One multilayer sheet may be used for each cartridge, or alternatively, one large multi-layer sheet of sufficient size to seal all four cartridges may be used. If one large sheet is used, a knife or some similar cutting tool may be used to cut the multi-layer sheet to separate each of the cartridges.

In step 140 of the process 100, each of the cartridges is loaded into a slot 18 of the thermal block 16 using an automated robotic handler, and in step 150, the samples are thermally cycled in accordance with a predetermined thermal profile. The samples are then removed from the thermal block and are subjected in step 160 to one or more evaluations. In the process described above, automated robotic handlers are used to transport the cartridges 20. As understood by those skilled in the art, the process may also be performed by an operator manually.

The apparatus and methods of the present invention described above provide several advantages over the prior art. First, cartridges are provided that allow standard automated processing equipment to be used to fill sample wells, and allow thermal blocks, designed for microscope slides, to be used to subject the samples to thermal cycling. Second, unlike typical prior art 96-well vessels, cartridges in accordance with embodiments of the present invention have a flat, thin bottom allowing optical analysis of samples through the bottom of the cartridge using known optically based detection systems. Third, single 384-well vessels of the prior art allow 384 wells to be cycled simultaneously. In contrast, a twin tower thermal block having 32 openings in each tower to accommodate a 96-well cartridge in accordance with embodiments of the present invention can provide thermal cycling for 3072 samples simultaneously, while maintaining a standard linear density of sample wells to allow the use of standard automated filling and analysis equipment..

In conical shaped wells of prior art vessels, sample volumes are typically approximately 100 μl and the wells provide a volume to surface ratio of 1.0 mm. In one embodiment of the present invention, the wells of the cartridges are designed to allow sample volumes of approximately 10 μl, while providing a volume to surface ratio of approximately 0.5 mm. With other relevant factors being equal, this should be expected to represent a reduction of the thermal time constant of the system by a factor of two when compared to typical conical-shaped wells. A reduction in thermal time constant reduces the time required to thermally cycle a sample, and for procedures requiring numerous thermal cycles for each sample, this is a significant advantage. Further, a lower volume to surface ratio generally provides a more consistent temperature throughout the entire sample during thermal cycling.

There are prior art devices that provide for multiple sample wells on a microscope slide. Typically, these devices create wells by positioning a matrix frame on top of a standard microscope slide. Embodiments of the present invention differ from these prior art devices in that, an array of wells are formed in a microscope slide format substrate by molding or drilling the wells into the substrate. While there are some prior art substrates that have depressions or concavities ground or molded into them, typically, these concavities are sections of a sphere having diameters of approximately 1 cm and depths of approximately 1-2 mm. One such device is available from Fisher Scientific of Hampton, NH, as part number 12-565B2.

In an embodiment of the invention described above, each cartridge 20 has 96 wells arranged in a 6 by 16 well array. In other embodiments, each cartridge may have a greater number of wells, however, it is preferred that the center-to-center spacing between wells be

maintained at 9 mm or some fractional value thereof to allow processing of the samples using standard automated equipment designed for 9 mm center-to-center spacing of sample wells. When other automated equipment is used for processing samples, the well spacing may be some value other than 9 mm or a fractional value thereof. Table 1 below lists several examples of cartridges in accordance with different embodiments of the present invention having different center-to-center well spacing, and shows the total number of available wells when four of the cartridges are combined in a cartridge holder such as cartridge holder 40 described above.

Table 1

Center-to-Center Spacing	Well Array Per Cartridge	Well Array For Four Cartridges	Total Wells For Four Cartridges in Holder
9 mm	8 x 3	8 x 12	96
4.5 mm	16 x 6	16 x 24	384
3 mm	24 x 9	24 x 36	864
2.25 mm	32 x 12	32 x 48	1536

In embodiments of the present invention discussed above, sample wells are described as being used for polymerase chain reactions and primed *in situ* synthesis. In other embodiments, the cartridges 24 may have ligands, such as oligonucleotides, attached within one or more of the sample wells.

Having thus described at least one illustrative embodiment of the invention, various alterations, modifications and improvements will readily occur to those skilled in the art. Such alterations, modifications and improvements are intended to be within the scope and spirit of the invention. Accordingly, the foregoing description is by way of example only and is not intended as limiting. The invention's limit is defined only in the following claims and the equivalents thereto.

CLAIMS

1. A cartridge for containing samples, the cartridge comprising:

a body having an upper surface with a length and width, each of which is approximately equal to a length and a width of a standard microscope slide; and

a plurality of wells formed within the upper surface of the body.

2. The cartridge of claim 1, wherein a center-to-center spacing between each pair of adjacent wells in the plurality of wells is approximately one of 9 mm, an integral fraction of 9 mm, and an integral multiple of 9 mm.

3. The cartridge of claim 2, wherein each of the wells is at least 2.4 mm deep.

4. The cartridge of claim 3, wherein each of the wells has a raised rim such that grooves are formed on the upper surface between the wells.

5. The cartridge of claim 4, wherein each of the wells has a flat, transparent bottom to permit optical inspection of samples contained within the wells.

6. The cartridge of claim 5, wherein a bottom surface of each of the wells is less than 0.75 mm thick.

7. The cartridge of claim 6, wherein the wells are arranged in a 6 by 16 array.

8. The cartridge of claim 7, further comprising a cover that seals each of the wells.

9. The cartridge of claim 8, wherein the cover is deformable to fill in the grooves between each of the wells.

10. The cartridge of claim 9, wherein the cover is a multi-layer sheet having a stiff backing layer, and a deformable layer.

11. The cartridge of claim 10, wherein the cover is transparent to allow optical inspection of samples in the wells through the cover.

12. The cartridge of claim 11, wherein the body is constructed using a material that is capable of withstanding a temperature of 100°C and a pressure of 1 atm.

13. The cartridge of claim 12, further comprising a handle section having a thickness less than a thickness of a portion of the upper surface containing the wells.

14. The cartridge of claim 1, wherein each of the wells has a raised rim such that grooves are formed on the upper surface between the wells.

15. The cartridge of claim 1, wherein each of the wells has a flat, transparent bottom to permit optical inspection of samples contained within the wells.

16. The cartridge of claim 1, wherein the wells are arranged in a 6 by 16 array.

17. The cartridge of claim 1, further comprising a cover that seals each of the wells.

18. The cartridge of claim 17, wherein the cover is deformable to fill grooves between each of the wells.

19. The cartridge of claim 18, wherein the cover is a multi-layer sheet having a stiff backing layer, and a deformable layer.

20. The cartridge of claim 17, wherein the cover is transparent to allow optical inspection of samples in the wells through the cover.

21. The cartridge of claim 1, further comprising a handle section having a thickness less than a thickness of a portion of the upper surface containing the wells.

22. The cartridge of claim 8, wherein the cover is attached to the cartridge using a hinge.

23. A cartridge holder comprising:
a frame having an upper surface; and

a plurality of cartridges disposed on the upper surface, each of the cartridges including:

a body having an upper surface with a length and width; and

a plurality of wells in the upper surface of the body; and

wherein the plurality of cartridges are arranged on the upper surface of the frame such that the wells of the cartridges form a continuous grid.

24. The cartridge holder of claim 23, wherein in at least one of the cartridges, a center-to center spacing between each pair of adjacent wells in the plurality of wells is approximately one of 9 mm, an integral fraction of 9 mm, and an integral multiple of 9 mm.

25. The cartridge holder of claim 24, wherein the center-to-center spacing of wells in the grid is approximately one of 9 mm, an integral fraction of 9 mm, and an integral multiple of 9 mm.

26. The cartridge holder of claim 25, wherein four cartridges are disposed on the upper surface of the frame.

27. The cartridge holder of claim 26, wherein the length and width of each body is approximately equal to a length and width of a standard microscope slide.

28. The cartridge holder of claim 27, wherein the wells of each of the cartridges are arranged in a 6 by 16 grid, and wherein the wells of all the cartridges are arranged in a 16 by 24 grid.

29. The cartridge holder of claim 28, wherein the frame has a first side, a second side and a back side, each extending above the upper surface.

30. The cartridge holder of claim 29, wherein each of the wells is approximately 2.4 mm deep.

31. The cartridge holder of claim 30, wherein each of the wells has a raised rim such that grooves are formed between the wells.

32. The cartridge holder of claim 31, wherein each of the wells has a flat transparent bottom.

33. The cartridge holder of claim 32, wherein at least one of the cartridges has a handle section extending beyond the upper surface to allow the cartridge to be grasped for placement in and removal from the cartridge holder.

34. The cartridge holder of claim 33, wherein four cartridges are disposed on the upper surface of the frame.

35. The cartridge holder of claim 23, wherein the length and width of each body is approximately equal to a length and width of a standard microscope slide.

36. The cartridge holder of claim 23, wherein the wells of each of the cartridges are arranged in a 6 by 16 grid, and wherein the wells of all the cartridges are arranged in a 16 by 24 grid.

37. The cartridge holder of claim 23, wherein the frame has a first side, a second side and a back side, each extending above the upper surface.

38. The cartridge holder of claim 23, wherein each of the wells has a raised rim such that grooves are formed between the wells.

39. The cartridge holder of claim 23, wherein at least one of the cartridges has a handle section extending beyond the upper surface to allow the cartridge to be grasped for placement in and removal from the cartridge holder.

40. A method of thermal cycling samples comprising steps of:

loading a plurality of cartridges into a cartridge holder, each of the cartridges having a plurality of wells arranged in a first grid;

filling each of the wells with a sample;

loading each of the cartridges into a thermal block;

subjecting the samples to thermal cycling;

removing the cartridges from the thermal block; and

analyzing the samples.

41 The method of claim 40, wherein the step of loading includes a step of arranging the cartridges in the cartridge holder such that the wells of the cartridges form a second grid.

42. The method of claim 41, wherein the second grid includes 384 wells arranged in a 16 by 24 array.

43. The method of claim 42, wherein the wells in the second grid have a center-to-center spacing of approximately one of 9 mm, an integral fraction of 9 mm, and an integral multiple of 9 mm.

44. The method of claim 40, wherein each of the cartridges has a length and width each of which is approximately equal to a length and width of a standard microscope slide.

45. The method of claim 40, wherein each of the wells has a transparent flat bottom, and wherein the step of analyzing includes a step of optically inspecting the samples through the bottom of the well.

46. The method of claim 40, further comprising a step of sealing each of the wells using a cover.

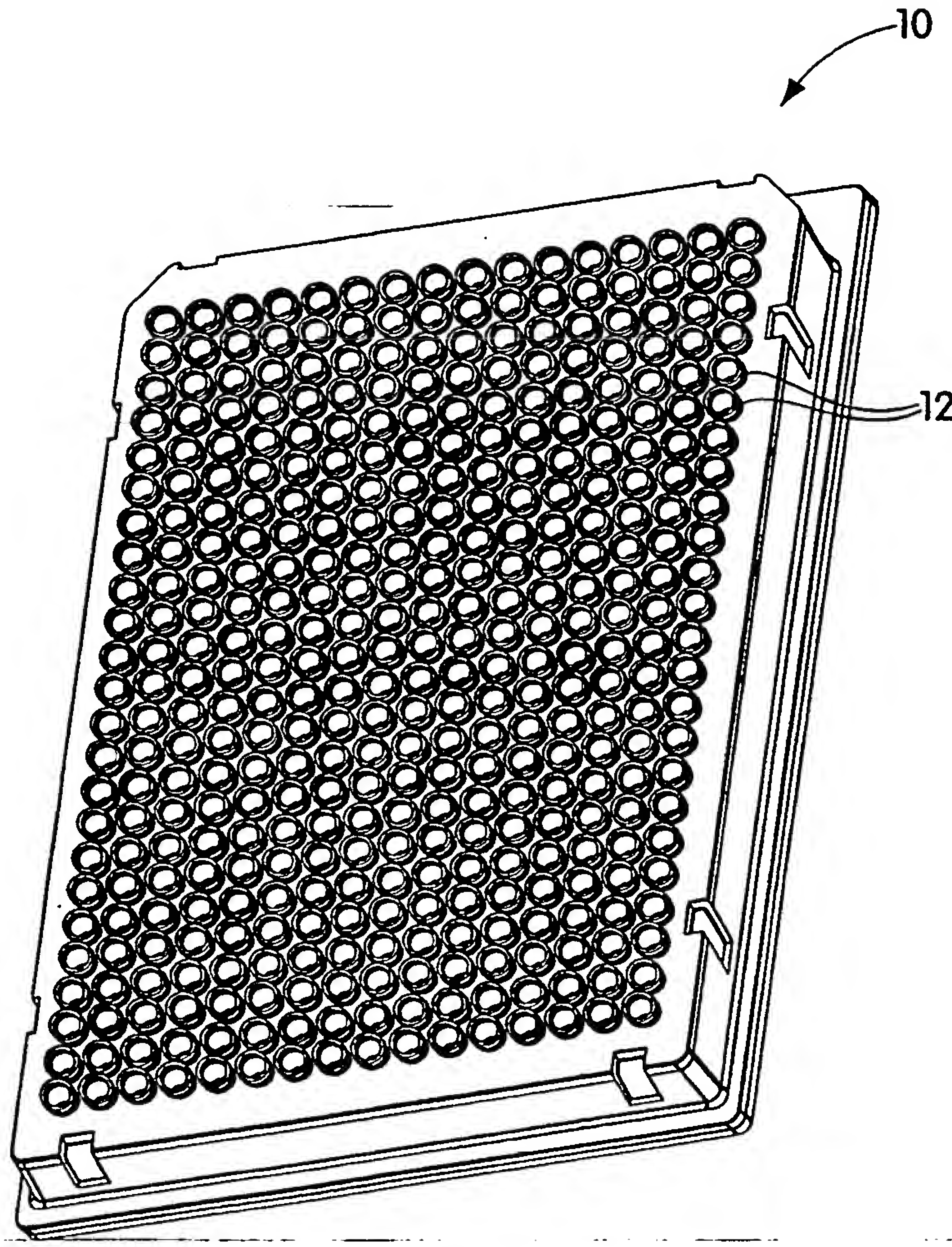

Fig. 1A

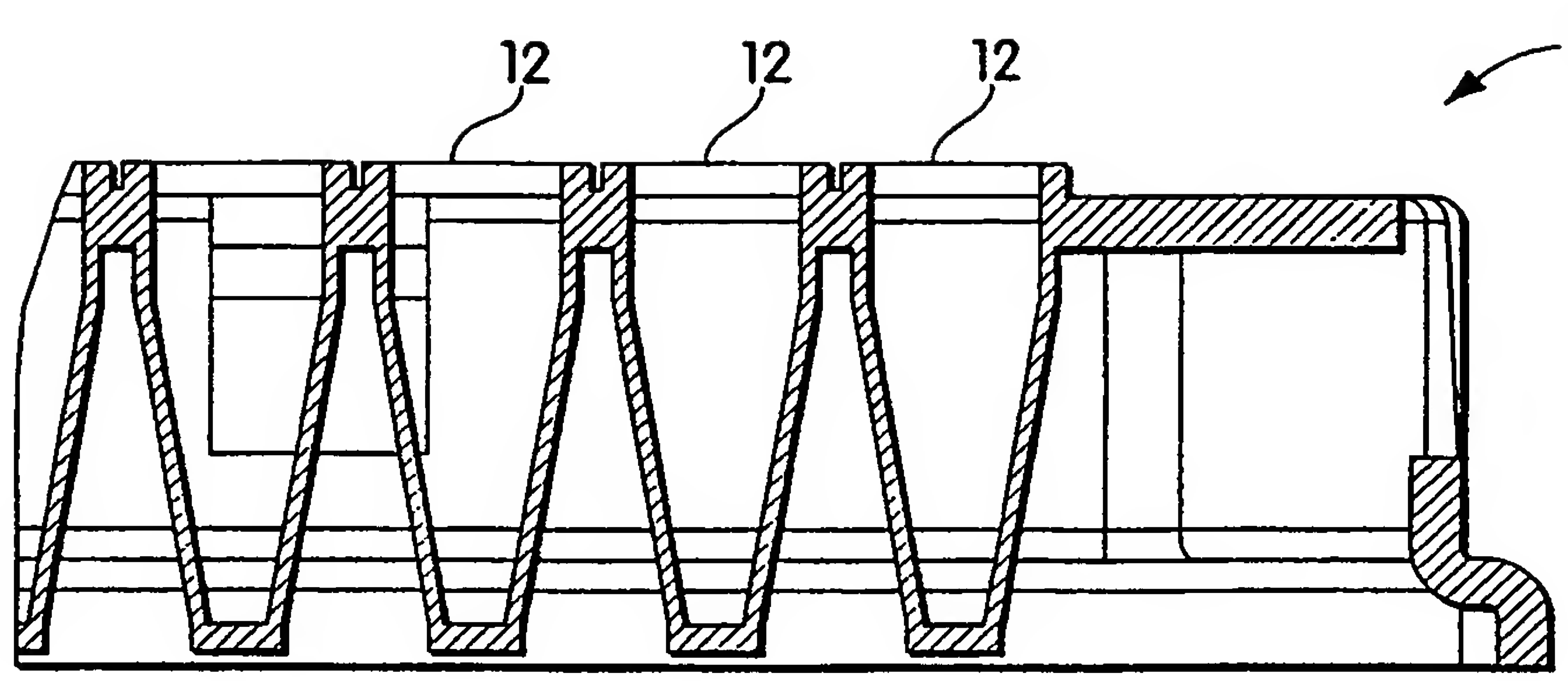

Fig. 1B

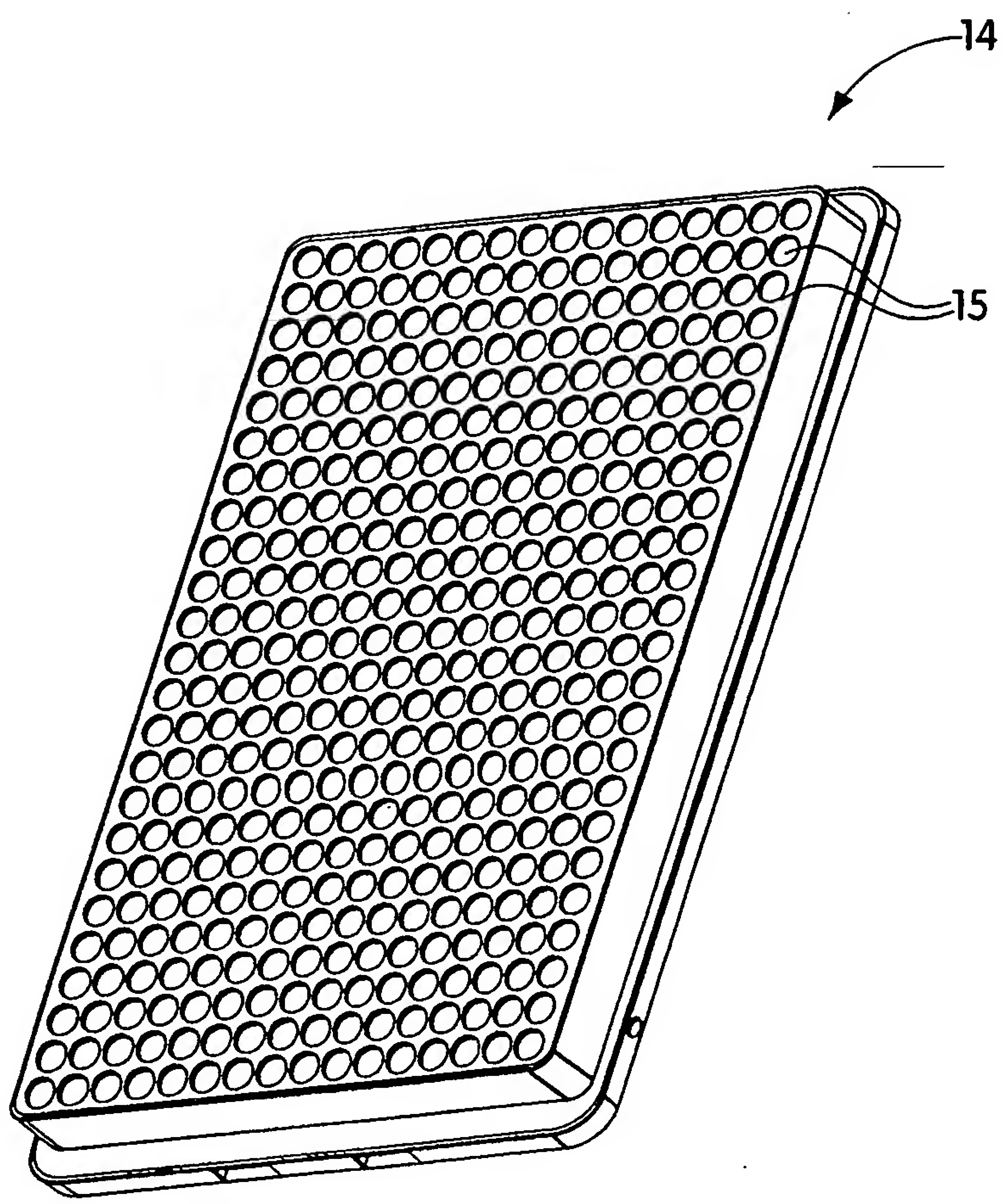

Fig. 1C

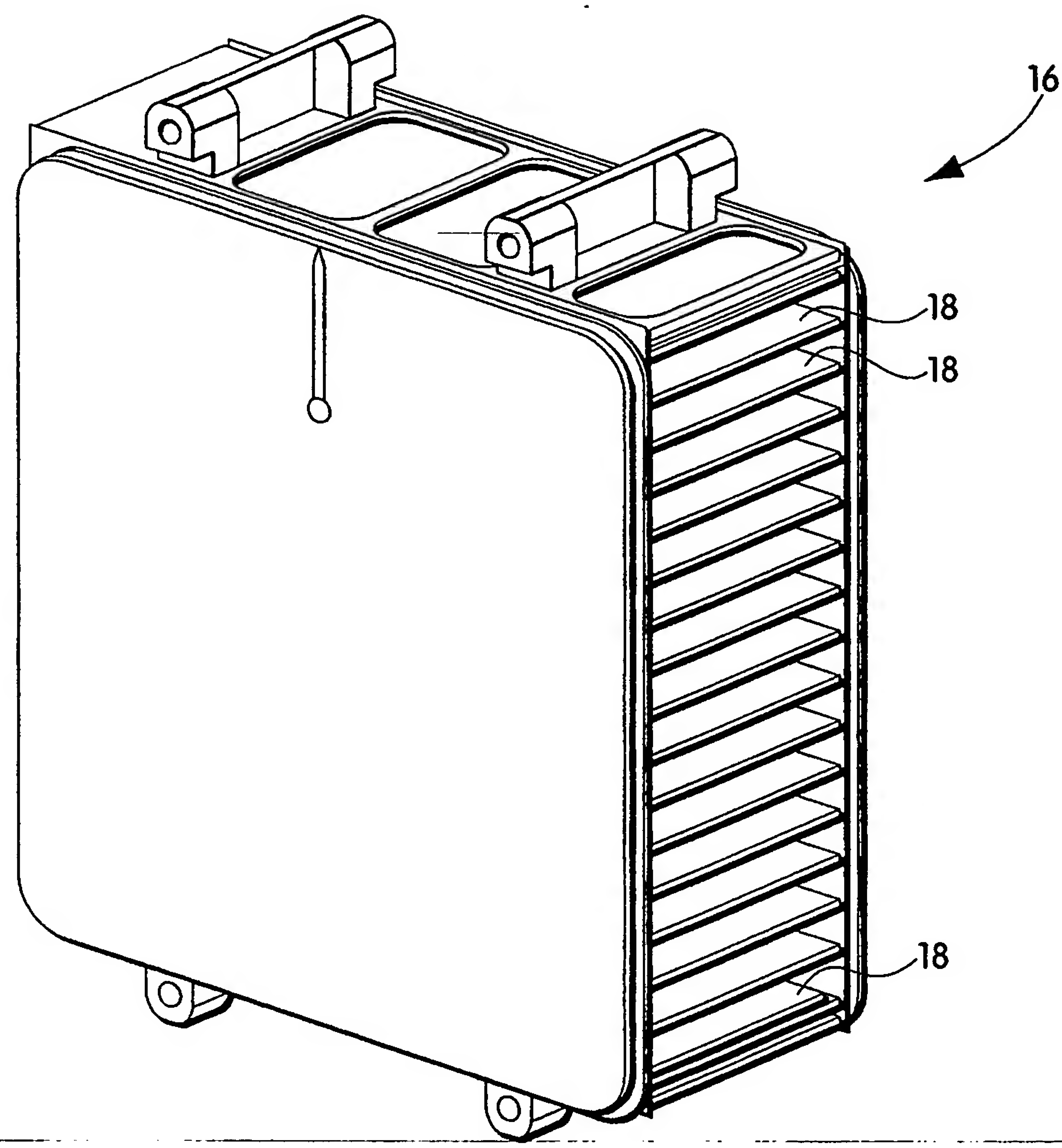

Fig. 2

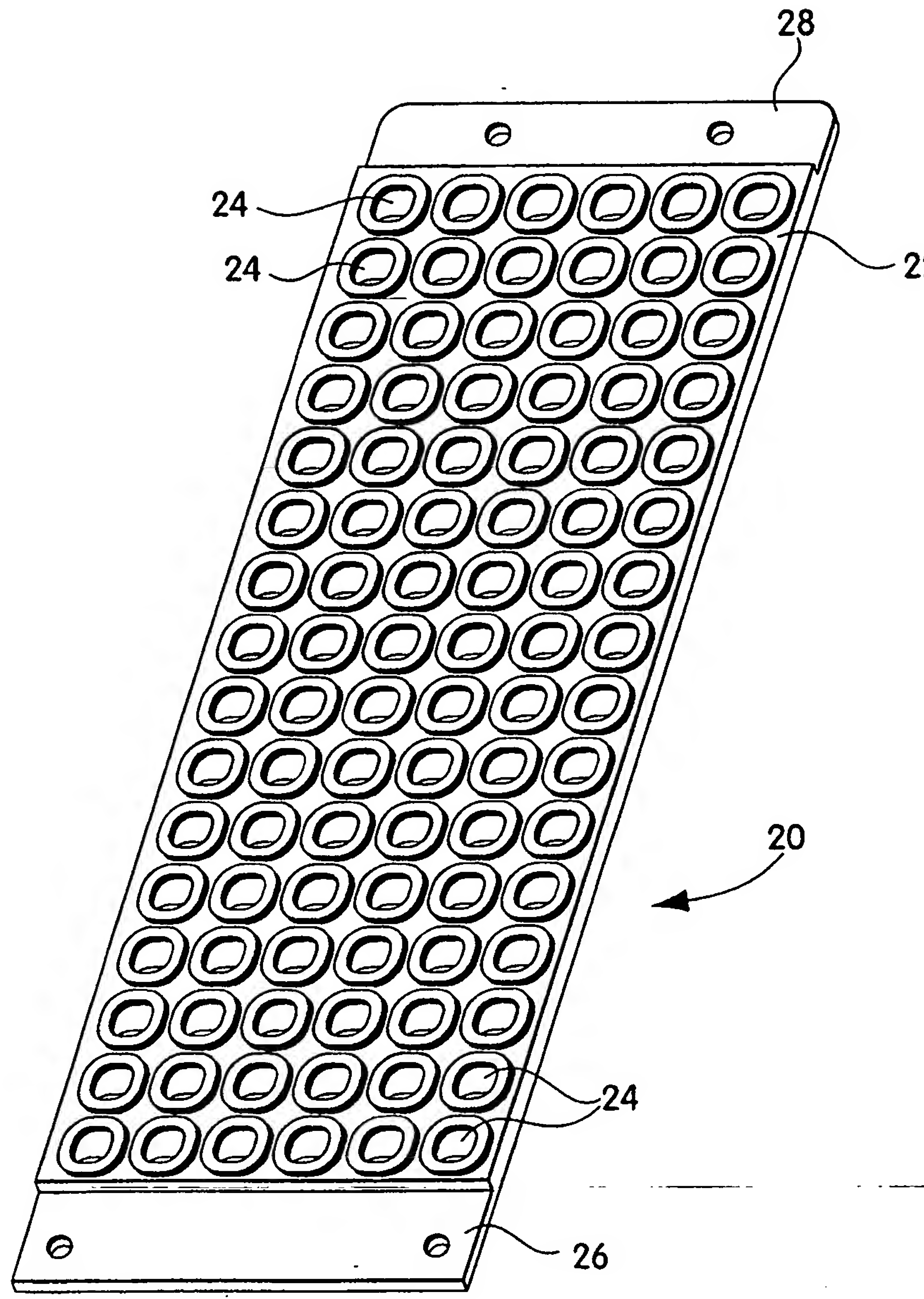

Fig. 3

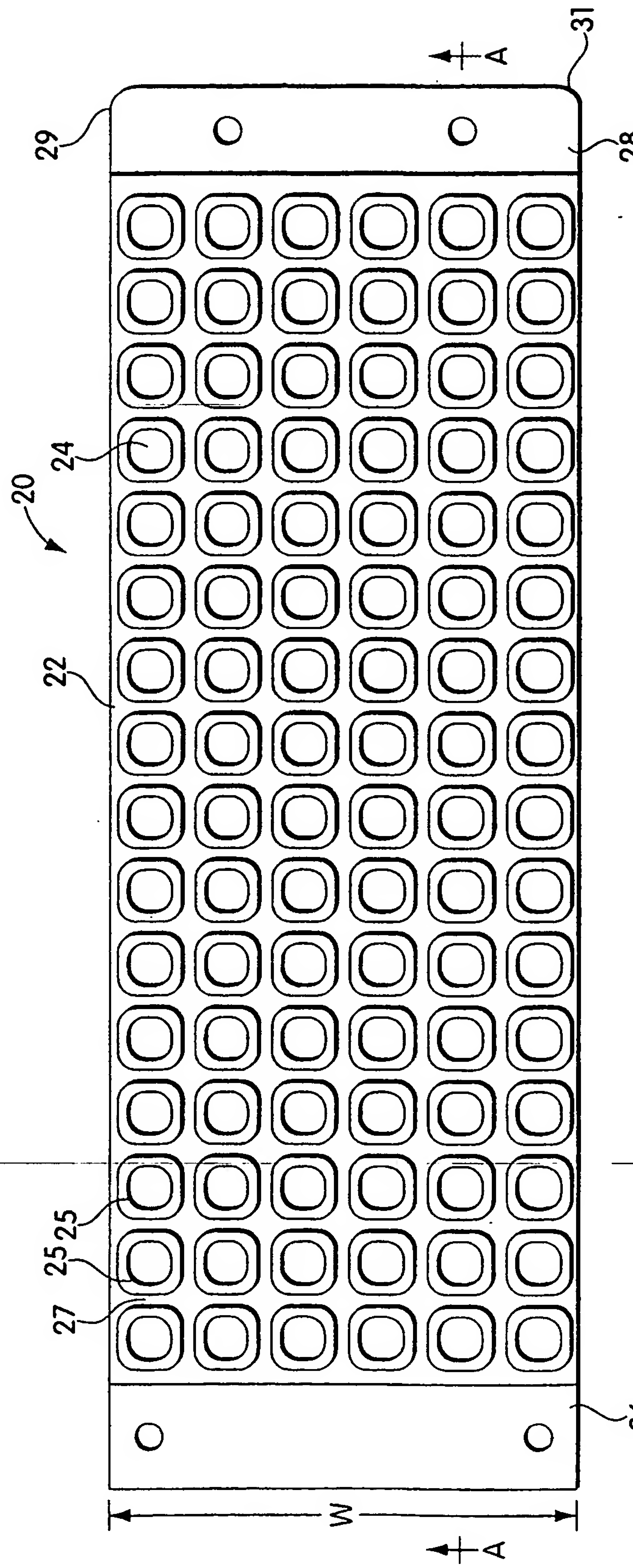

Fig. 4

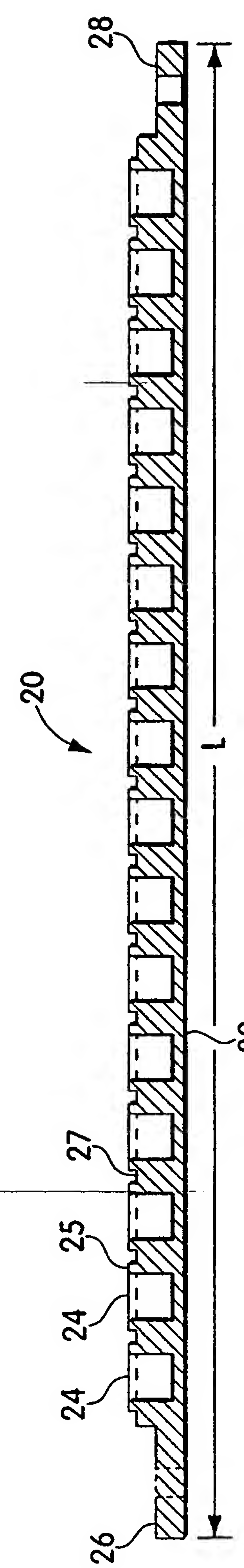

Fig. 5

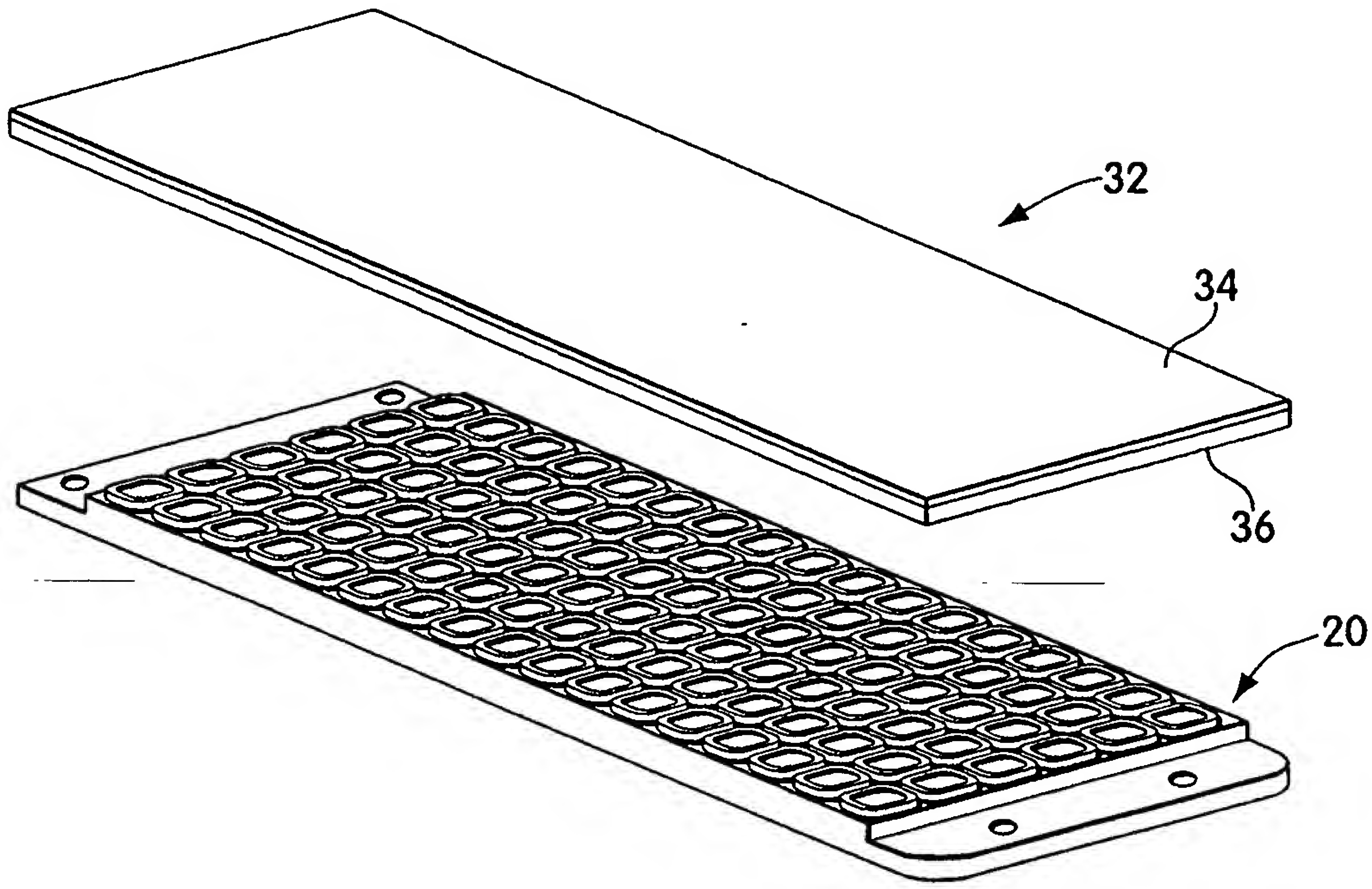

Fig. 6A

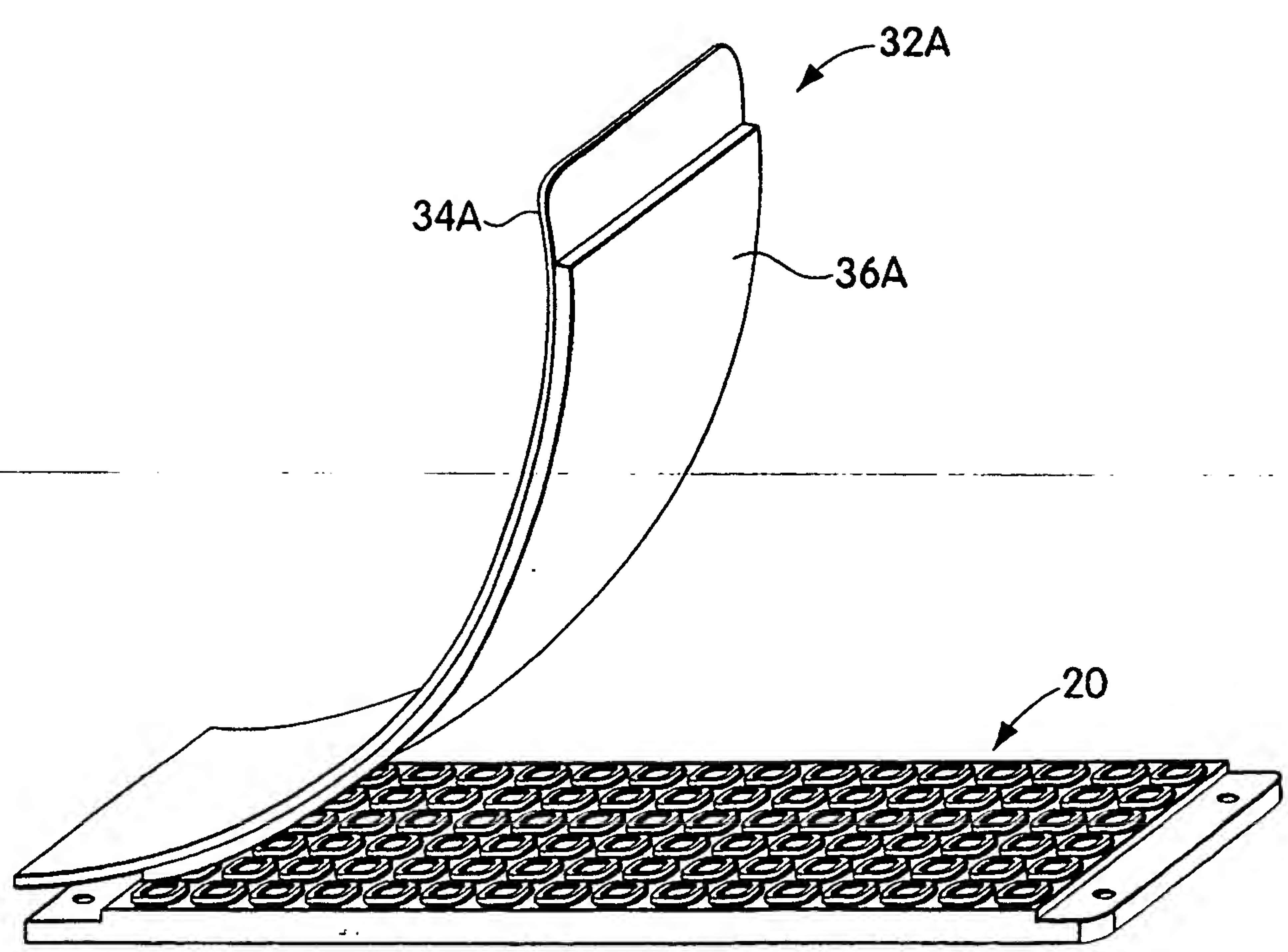

Fig. 6B

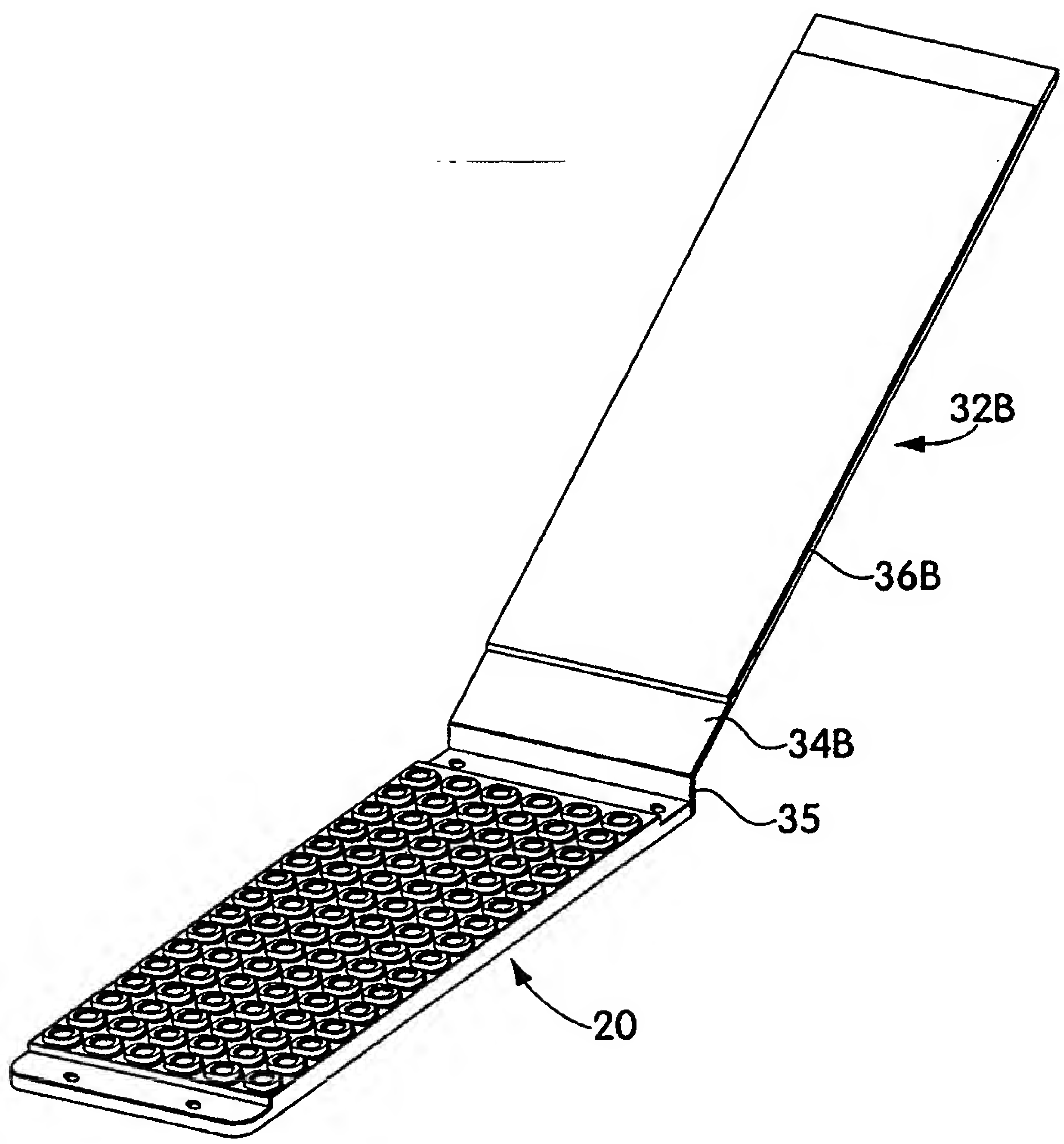

Fig. 6C

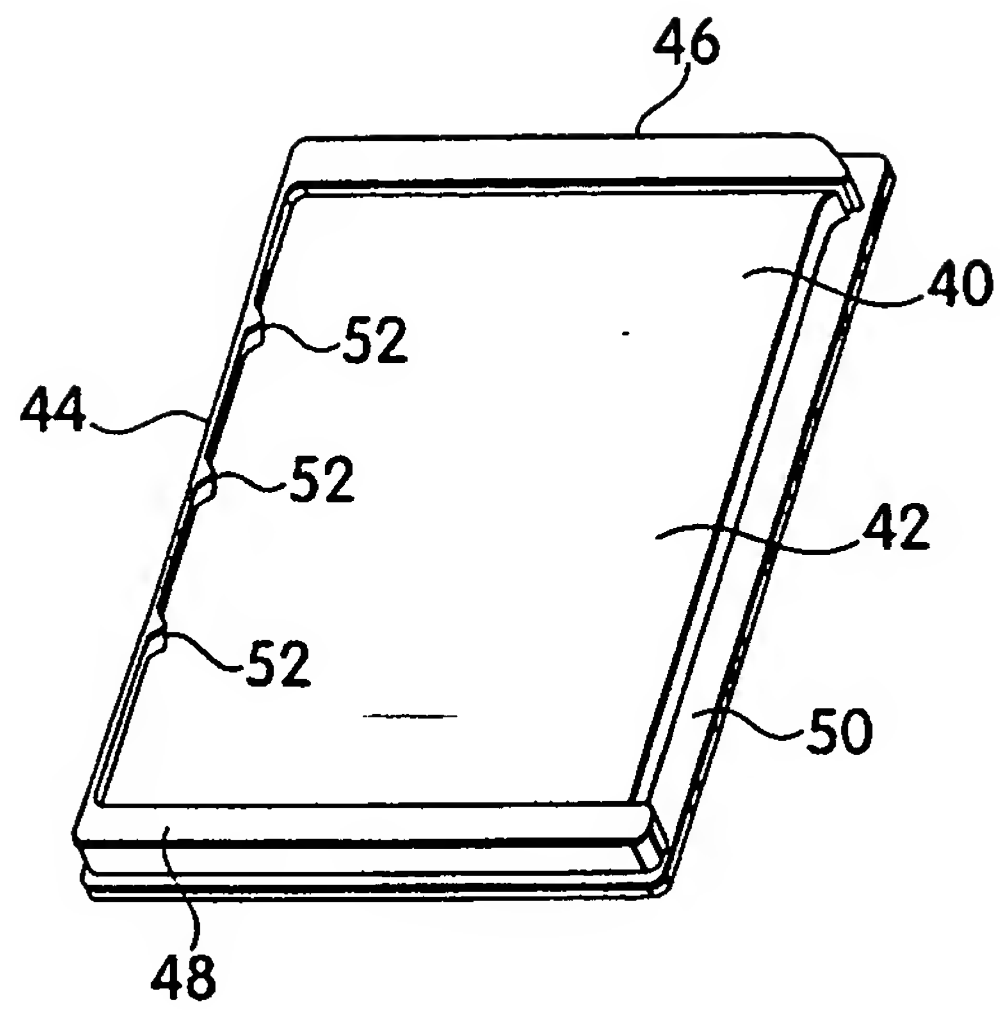

Fig. 7

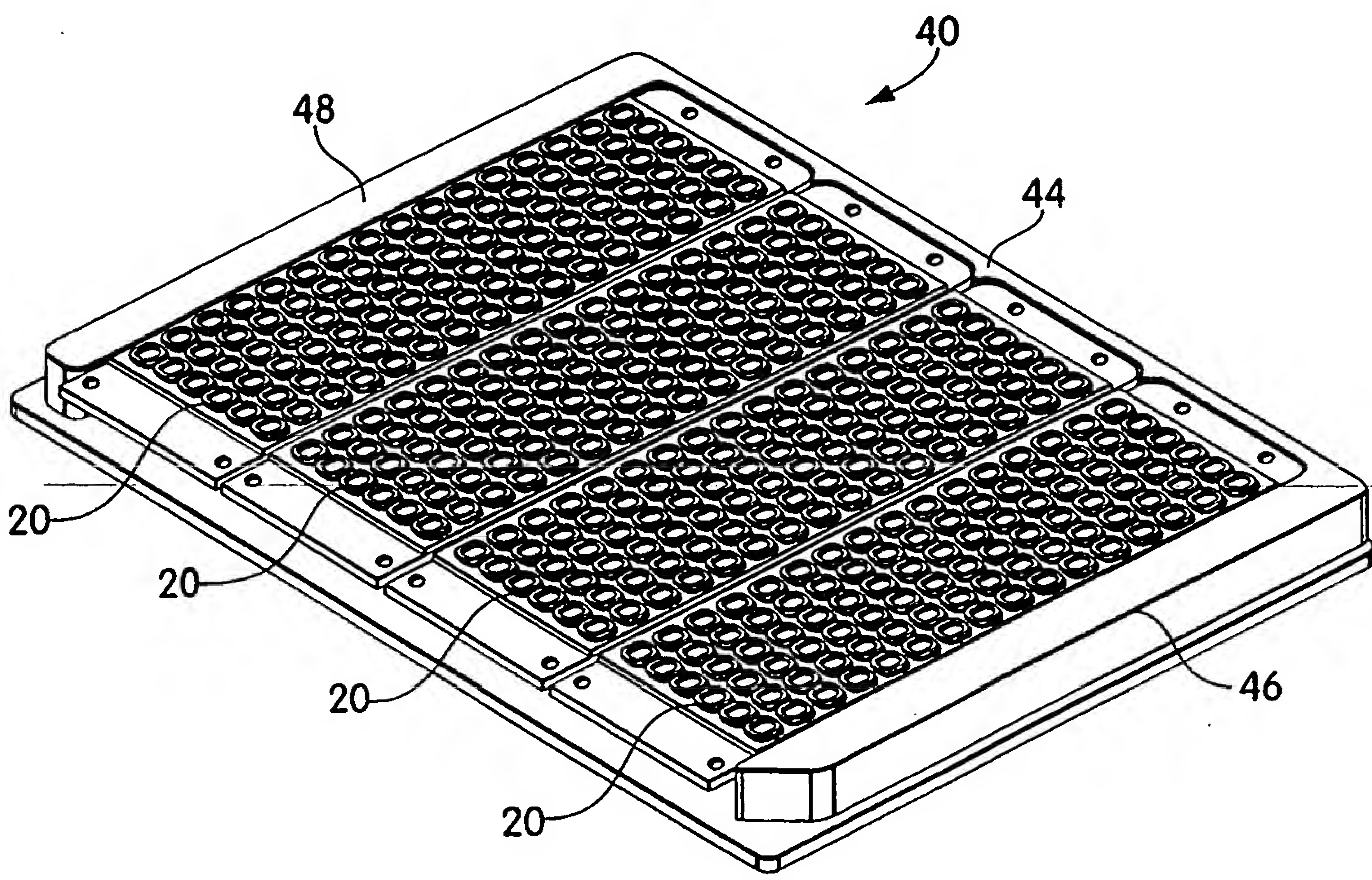

Fig. 8

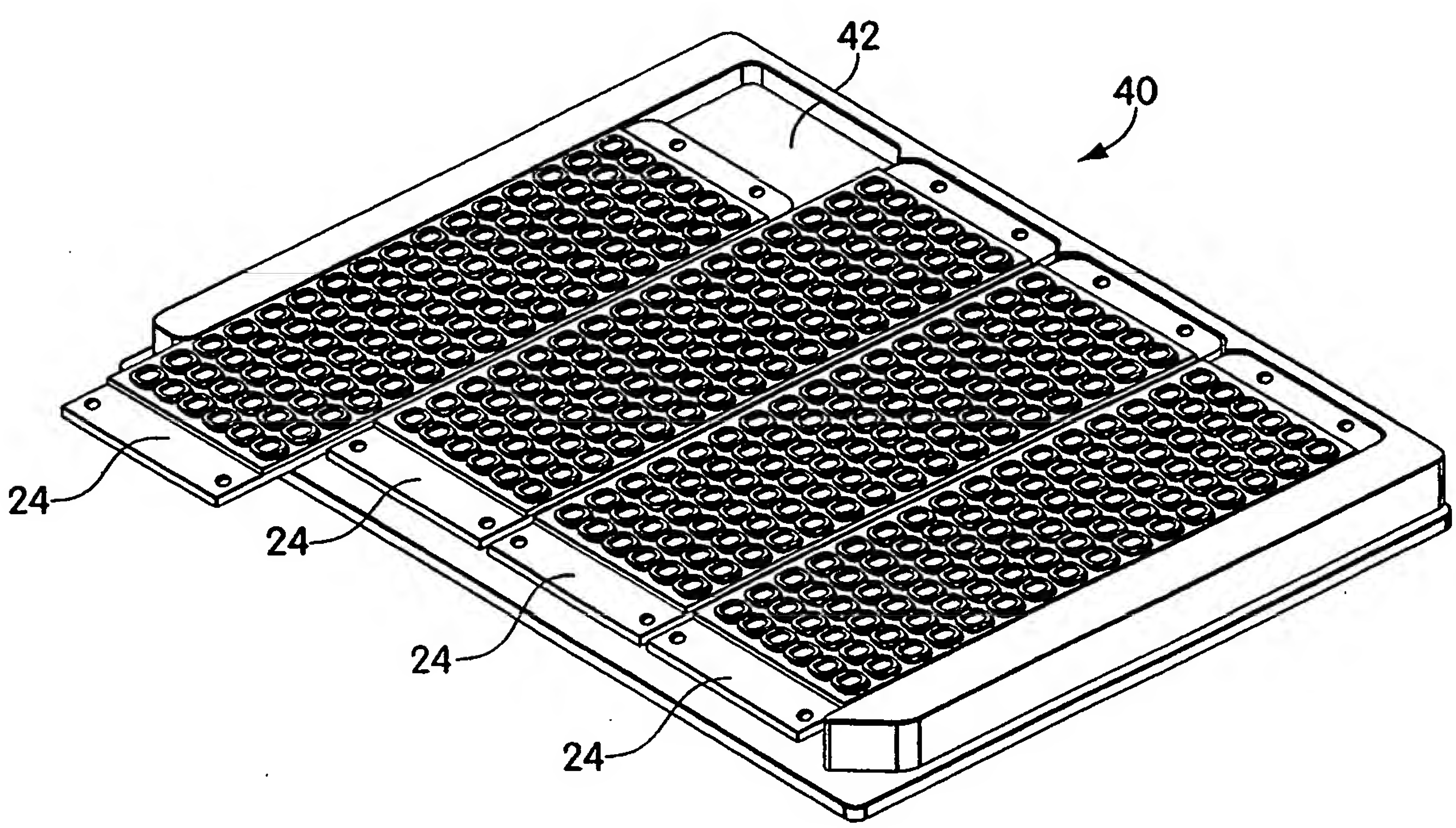

Fig. 9

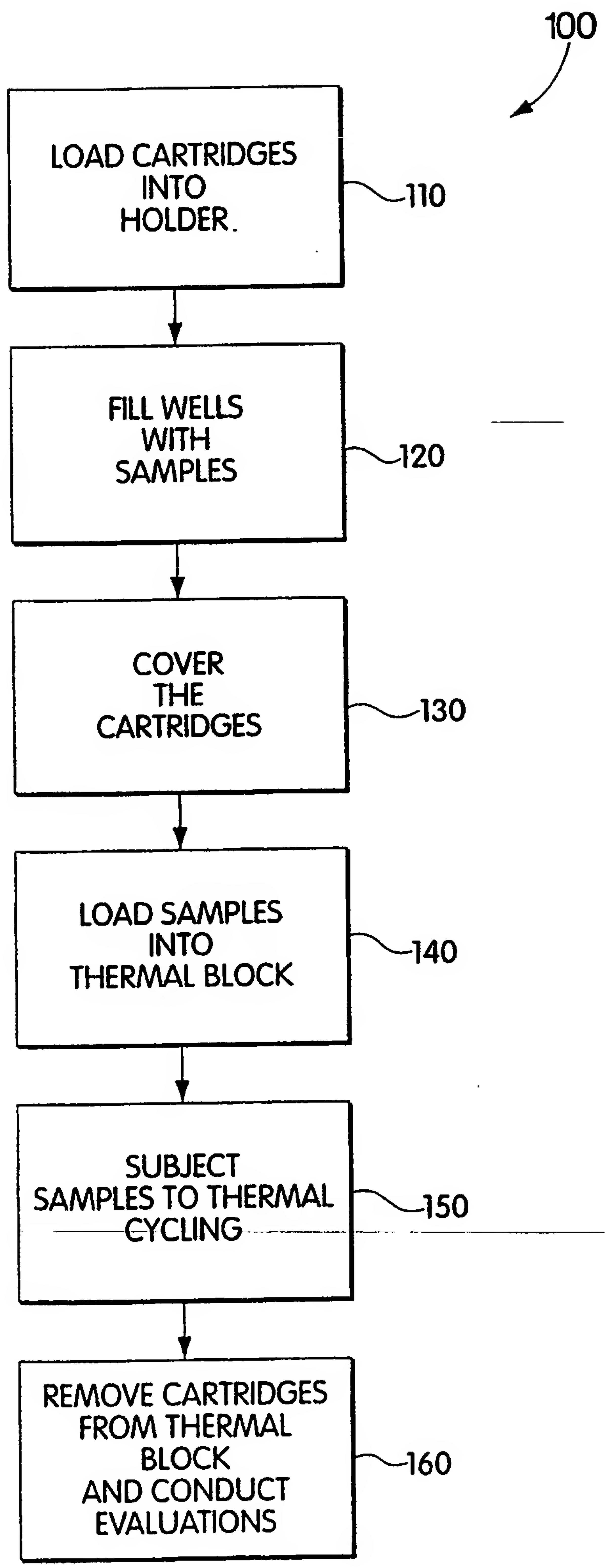
100
LOAD CARTRIDGES INTO HOLDER.
110
FILL WELLS WITH SAMPLES
120
COVER THE CARTRIDGES
130
LOAD SAMPLES INTO THERMAL BLOCK
140
SUBJECT SAMPLES TO THERMAL CYCLING
150
REMOVE CARTRIDGES FROM THERMAL BLOCK AND CONDUCT EVALUATIONS
160

Fig. 10

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11452

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00 G02B21/34 B01L9/00 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L G02B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 545 673 A (SEIKAGAKU KOGYO CO LTD) 9 June 1993 (1993-06-09) column 1, line 9 - line 13; figures 2,4 column 4, line 15 - line 17	5,15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
6 September 1999	16/09/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11452

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X	page 10, line 33 - page 11, line 1	17-19
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